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Adoptive Immunotherapy by Allogeneic Stem Cell Transplantation for Metastatic Renal Cell Carcinoma: A CALGB Intergroup Phase II Study

Brian I. Rini,[1] Susan Halabi,[2] Robert Barrier,[3] Kim A. Margolin,[4] David Avigan,[5] Theodore Logan,[6] Walter M. Stadler,[7] Philip L. McCarthy,[8] Charles A. Linker,[1] Eric J. Small,[1] for the Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, and Southwestern Oncology Group

[1]Department of Medicine, University of California San Francisco Cancer Center, San Francisco, California; [2]Department of Biostatistics and Biostatistics, Duke University Medical Center, Durham, North Carolina; [3]Cancer Center Biostatistics, Duke University Medical Center, Durham, North Carolina; [4]Division of Medical Oncology/Hematology and Hematopoietic Cell Transplant, City of Hope Medical Center, Duarte, California; [5]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [6]Indiana University Cancer Center, Indianapolis, Indiana; [7]Department of Medicine, University of Chicago, Chicago, Illinois; [8]Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York

Correspondence and reprint requests: Brian I. Rini, MD, Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Center, 9500 Euclid Avenue, Desk R35, Cleveland, OH 44195 (e-mail: rinib2@ccf.org).

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ABSTRACT

A graft-versus-tumor effect through nonmyeloablative allogeneic stem cell transplantation (N-SCT) in metastatic renal cell carcinoma (RCC) has been reported. An Intergroup phase II trial was undertaken to define further the feasibility, toxicity and efficacy of this approach in a multi-institutional setting, Patients with cytokine-refractory, metastatic RCC were treated with N-SCT. The conditioning regimen was fludarabine 30 mg · m^{-2} · d^{-1} on day (d) −7 through d −3 and cyclophosphamide 60 mg · kg^{-1} · d^{-1} on d −4 and d −3. Patients received 2-8 × 10^6 $CD34^+$ cells/kg of granulocyte colony-stimulating factor mobilized stem cells from a 6/6 HLA-matched sibling donor. Immunosuppression after transplantation included tacrolimus and methotrexate. Twenty-two patients were enrolled at 14 institutions. Greater than 90% donor T-cell chimerism was observed in 17 of 19 evaluable patients (89%) by d +120. No objective response was observed. Acute graft-versus-host disease (GVHD) was observed in 11 patients (50%). Chronic GVHD was reported in 5 patients (23%). There was 1 patient death from liver failure secondary to chronic GVHD. Regimen-related mortality was 2 of 22 (9%; liver failure, sepsis). Median survival time was 5.5 months (95% confidence interval, 3.9-12.0 months) and the median time to progression was 3.0 months (95% confidence interval, 2.3-4.2 months). N-SCT for metastatic RCC is feasible in a multi-institutional setting. Adequate donor T-cell engraftment was achieved in most patients before disease progression. A graft-versus-tumor effect was not observed in this study despite acute and chronic GVHD, thus highlighting the need for further understanding of this approach. Allogeneic SCT remains investigational in RCC.

KEY WORDS

Renal cell carcinoma • Nonmyeloablative transplant • Allogeneic

INTRODUCTION

Metastatic renal cell carcinoma (RCC) currently is a largely incurable disease with few effective treatment options. Immunotherapy including interleukin-2 and/or interferon-α is standard initial treatment in metastatic RCC, but these agents have limited effects on RCC tumor progression in most patients [1]. Investigators have thus attempted to improve on immunotherapy in a myriad of ways including combination cytokine therapy [2,3], administration of immunologically active cells such as lymphokine-activated killer

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cells [4,5], or tumor-infiltrating lymphocytes [6]. Each of these strategies sought to generate an antitumor immune response, but none resulted in significant clinical benefit. Investigation into alternative forms of inducing an antitumor immune response in RCC is thus warranted.

One such immunotherapeutic maneuver that has been applied to metastatic RCC is nonmyeloablative allogeneic stem cell transplantation (N-SCT). This procedure involves administration of an immunosuppressive conditioning regimen that allows for engraftment of blood or bone marrow stem cells from a histocompatible donor. Donor T lymphocytes recognize recipient tissue antigens as foreign and generate a graft-versus-host (GVH) reaction called GVH disease (GVHD). GVHD results in inflammation in target organs, primarily skin, liver, and gastrointestinal tract. GVHD can be accompanied by a graft-versus-tumor (GVT) effect due to the recognition of host tumor cells by donor cells as foreign and can result in recipient tumor regression. N-SCT has been described for metastatic RCC using mainly sibling donors with preliminary evidence of antitumor activity in several single institution studies (Table 1) [7-15]. Of note, these studies enrolled patients with nonuniform baseline characteristics, employed variable conditioning and immunosuppression regimens after transplantation, and included small patient numbers. It may be surmised from these series, however, that a graft-versus-RCC effect can be induced by N-SCT and is balanced against toxicity including GVHD and transplant-related mortality. The limitations of these studies have hampered the ability to precisely estimate the relative risks and benefits of this approach in metastatic RCC.

Based on these considerations, a study of N-SCT in metastatic RCC was undertaken to define the feasibility, safety, and efficacy of this approach when performed in a multi-institutional setting.

Table 1. *Major Series of Sibling Donor, Nonmyeloablative Allogeneic Stem Cell Transplantation in Metastatic Renal Cell Carcinoma*

Study	Patients, n	Objective Response Rate*	GVHD†	TRM‡
Childs et al [7]	19	53%	74%	12%
Rini et al [8], Artz et al [9]	18	22%	50%	14%
Bregni et al [10]	7	57%	86%	0%
Pedrazolli et al [11]	7	0%	0%	29%
Ueno et al [12]	15	20%	60%	20%
Nakagawa et al [13]	9	11%	56%	0%
Massenkeil et al [14]	6	33%	67%	0%
Tykodi et al [15]	8	13%	63%	0%

*Complete or partial tumor response.
†Percentage of patients with acute and/or chronic GVHD.
‡Transplant-related mortality defined as non–disease-related patient deaths before day +100.

METHODS

Eligible patients had histologically confirmed metastatic RCC of clear cell or papillary subtype with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria [16]. Patients must have received previous therapy for metastatic RCC consisting of interluekin-2 and/or interferon-α with disease progression or intolerance of therapy. Other previous systemic therapy was permitted but not required. Patient age ≤60 years, life expectancy >6 months, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were required. An HLA-identical sibling donor was required. Patients had normal organ and marrow function as defined by a granulocyte count ≥1500/μL, platelet count ≥100 000/μL, total bilirubin level ≤2 × institutional upper limit of normal, aspartate aminotransferase level ≤3 × institutional upper limit of normal, and creatinine clearance ≥40 mL/min (calculated by Cockcroft-Gault formula). Adequate cardiac function as defined by a left ventricular ejection fraction ≥45% by echocardiogram or Multiple Gated Acquisition Scan and adequate pulmonary function as defined by Diffusion Capacity of the Lung for Carbon Monoxide >40% of expected value corrected for hemoglobin level were required.

Patients who had received any systemic therapy for RCC within 4 weeks or radiotherapy within 2 weeks before entering the study were excluded. Patients with any current or previous central nervous system metastases were excluded. All patients underwent brain magnetic resonance imaging before enrollment to exclude central nervous system metastatic disease. Patients with uncontrolled diabetes, active serious infection, pregnancy/nursing, known hypersensitivity to *Escherichia coli*-derived product, or known positivity for human immunodeficiency virus were excluded. Patients were not permitted to have a currently active second malignancy. Second malignancies were not considered currently active if the patient had completed therapy and was considered to be at <30% risk of relapse. All patients signed a written protocol-specific informed consent approved by their institutional review board.

Sibling donors were HLA-identical (6/6) by serologic typing (for class 1 antigens) and molecular typing (for class 2 antigens). Syngeneic donors, <6/6 sibling donors, matched unrelated donors, and haploidentical donors were excluded. All donors were healthy and met each bone marrow transplantation center institutional requirements for stem cell donation including testing for human immunodeficiency virus, hepatitis, and syphilis. Donors received granulocyte colony-stimulating factor (Neupogen, Amgen, Thousand Oaks, Calif) before leukapheresis and had no significant cardiopulmonary, renal, endocrine, or hepatic disease. In addition, donors could not be pregnant or have a previous malignancy except nonmelanoma skin

cancer, cervical carcinoma in situ, superficial bladder cancer, or stage I or II cancer that was adequately treated and currently in remission. All donors signed a written protocol-specific informed consent approved by their institutional review board.

Treatment

Patients received a conditioning regimen consisting of fludarabine 30 mg $\cdot$ m^{-2} $\cdot$ d^{-1} intravenously (IV) on day (d) -7 (7 days before stem cell infusion) through d -3 and cyclophosphamide 60 mg $\cdot$ kg^{-1} $\cdot$ d^{-1} IV on d -4 and d -3 based on previous experience with a similar conditioning regimen in RCC [7]. Chemotherapy doses were based on corrected body weight, calculated as .25 $\times$ [(actual weight $-$ ideal weight) + ideal weight]. Allogeneic peripheral blood stem cells were infused at a dose of 2-8 $\times$ 10^6 $CD34^+$ cells/kg (recipient actual weight) on d 0. Patients received granulocyte colony-stimulating factor 5 μg/kg subcutaneously starting on d +5 and continued until an absolute neutrophil count of .5 $\times$ 10^9/L was maintained for 3 consecutive days.

Pheresis of Allogeneic Donors

Stem cell donors received granulocyte colony-stimulating factor 10 μg $\cdot$ kg^{-1} $\cdot$ d^{-1} on d -5 through d -2 (and, if necessary, d -1). Beginning on day -1, daily vein-to-vein apheresis was performed on the donor to harvest peripheral blood stem cells until 2-8 $\times$ 10^6 $CD34^+$ cells/kg recipient body weight was achieved. An additional 6 $\times$ 10^7 donor $CD3^+$ cells/kg were allowed to be collected, frozen in 2 separate aliquots (1 $\times$ $10^7$and 5 $\times$ 10^7 $CD3^+$ cells/kg), and stored in liquid nitrogen for possible subsequent donor lymphocyte infusion (DLI).

GVHD Prophylaxis

Tacrolimus (FK506, Prograf; Astellas Pharma Inc, Deerfield, IL) was administered orally (or IV, if not tolerated) beginning on d -1 to maintain a serum trough level of 5-10 ng/mL. Tacrolimus was tapered over 30 days beginning on d +60 in the absence of GVHD. Patients with disease progression before d +60 could have tacrolimus tapered in the absence of GVHD. In addition, a methotrexate 5 mg/m^2 intravenous push was given on d +1, d +3, and d +6. Methotrexate was held in the event of a serum creatinine level >3.0 mg/dL and administered with leucovorin 10 mg IV every 6 hours for 4 doses if the serum creatinine level was 2.0-2.9 mg/dL.

Supportive Care

Patients with a history of herpes simplex infection or seropositivity received acyclovir 200-400 mg orally 3 times a day or valacyclovir 500 mg orally 1 time daily from d -3 to d +100. Fungal prophylaxis was undertaken with fluconazole or itraconazole 200-400 mg orally daily, voriconazole 200 mg orally 2 times daily, or low-dose amphotericin B (10-20 mg/day) on d +1 through d +100. *Pneumocystis carinii* pneumonia prophylaxis consisted of a trimethoprim-sulfamethoxazole (Bactrim, Roche, Nutley, NJ) double-strength tablet orally 2 times daily for 2 days weekly on d -3 through d +100. Patients with sulfa allergies could receive dapsone 100 mg orally 3 times a week or inhaled pentamidine. All prophylaxis could be extended beyond d +100 at the discretion of the treating physician. No prophylaxis for cytomegalovirus (CMV) was initiated. Surveillance for CMV was undertaken through detection of CMV antigen by polymerase chain reaction or enzyme-linked immunosorbent assay weekly $\times$ 8 beginning on d +7, every other week until d +98, and then as needed. Patients with CMV detected (positive CMV cultures or CMV antigen) received gancyclovir 5 mg/kg IV 2 times daily $\times$ 14 days. Management of acute and chronic GVHDs (ie, management of immunosuppressant medications) was at the discretion of the treating physician.

Donor Lymphocyte Infusion

Patients were eligible for up to 2 DLIs if they demonstrated disease progression while off all immunosuppression for $\geq$30 days without signs or symptoms of active GVHD. Patients received 1 $\times$ 10^7 $CD3^+$ cells/kg from the original HLA-identical sibling donor (from initial stem cell collection or through repeat leukapheresis). Patients with further disease progression were eligible for a second DLI of 5 $\times$ 10^7 $CD3^+$ cells/kg no sooner than 8 weeks after the first DLI. No post-DLI immunosuppression was given. Patients with disease progression after the second DLI were eligible to receive interferon-α, escalated from 1 million unit 3 times a week to a maximum of 9 million units 3 times a week.

Patient Assessment

All patients underwent computed tomography of the chest, abdomen, and pelvis and bone scanning within 28 days before registration. Computed tomography was repeated at d +60, d +120, d +180, and every 3 months thereafter. Bone scanning was repeated at the time of computed tomography only in patients with bone metastases or in patients who developed signs or symptoms of bone metastases while in the study. Donor chimerism for T cells ($CD3^+$), myeloid cells ($CD14/15^+$), and B cells ($CD19^+$) was assessed through amplification of informative variable number of tandem repeat or short tandem repeat domains on d +30, d +60, d +90, d +120, d +180, and every 3 months thereafter.

Table 2. *Patient Characteristics (n = 22)*

Age (y)*	**53 (39-60)**
Male†	**16 (73%)**
Female†	**6 (27%)**
ECOG performance status†	
0	**14 (64%)**
1	**8 (36%)**
Site of metastases‡	
Lung	**14 (64%)**
Lymph node	**15 (68%)**
Liver	**5 (23%)**
Bone	**11 (50%)**
Metastatic sites§	
1	**6 (27%)**
2	**6 (27%)**
≥3	**10 (45%)**
Prior local therapy‡	
Nephrectomy	**21 (95%)**
Radiotherapy (any)	**13 (59%)**
Prior systemic treatments§	
1	**13 (59%)**
2	**7 (32%)**
≥3	**1 (5%)**
Years from diagnosis to treatment‖	**1.5 (.7-2.1)**
Baseline hemoglobin (g/dL)	**13.9 (9.0-16.1)**
Baseline LDH (U/dL)	**177 (129-258)**

ECOG indicates ??; LDH, lactate dehydrogenase.
*Median (range).
†Number of patients (%).
‡Categories are not mutually exclusive.
§Number (%).
‖Median (interquartile range).

Statistical Design and Data Analysis

Sample size calculation was based on the primary endpoint (response rate). The null hypothesis was that the response rate (complete and partial remission) was ≤20% versus the alternative hypothesis that the response rate (complete and partial remission) was ≥40%. A single-stage design was used in which 36 patients with RCC would be accrued. This design had a type I error rate of .09 and 91% power. Patient registration and data collection were managed by the Cancer and Leukemia Group B Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson.

In addition, the study was monitored for unacceptable toxicity, defined as transplant-related mortality within the first 6 months after transplantation. In particular, if at any time during the course of the study, the observed percentage of transplant-related mortality exceeded 20% by ≥1 SE, accrual was to be immediately suspended. Survival time was calculated as the difference between the last follow-up date or date of death and the date of initiation of treatment on trial. Progression-free survival was defined as the interval between date of progression or death, whichever occurred first, and the date of treatment initiation. Overall survival and progression-free survival distributions were estimated with the Kaplan-Meier product-limit method.

RESULTS

Patient Characteristics

Between July 25, 2002 and April 5, 2004, 22 patients with metastatic RCC were enrolled at 14 institutions. After accrual of 22 patients, no objective response had been observed, and thus a futility analysis was performed. Because it was deemed unlikely, based on the results of this futility analysis, to accept the alternative hypothesis, the study was closed to further accrual. Most patients (64%) had an ECOG performance status 0 and 95% had undergone previous nephrectomy (Table 2). A substantial proportion of patients had received previous radiotherapy (59%) and/or had received ≥2 previous systemic regimens for metastatic RCC (37%). In addition, the median time from diagnosis of RCC to protocol therapy was short (1.5 years).

Engraftment

A median of 5.2×10^6 (range, $2.6\text{-}12.8 \times 10^6$) $CD34^+$ cells/kg and a median of 3.3×10^6 (range, $1.4\text{-}7.5 \times 10^6$) $CD3^+$ cells/kg were infused. Median time to neutrophil recovery ≥1000/μL was 12 days (range, 3-32). Median time to untransfused platelet recovery ≥50 000/μL was 15 days (range, 8-26). Engraftment data for major lineages are presented in Table 3. Nineteen patients were successfully tapered off tacrolimus per protocol. By d +120, 17 (89%; 95% confidence interval [CI], 67%-99%) of evaluable patients had achieved >90% donor T-cell chimerism and 16 patients (84%; 95% CI, 60%-97%) had achieved >95% donor T-cell chimerism. Engrafting failed in 1 patient who had autologous bone marrow recovery.

Table 3. *Engraftment*

	T Cells ($CD3^+$)	Myeloid Cells ($CD14/15^+$)	B Cells ($CD19^+$)
Median (range) donor chimerism at day +30	**94% (74%-100%)**	**56% (14%-100%)**	**87% (65%-100%)**
Median (range) donor chimerism at day +90	**98% (35%-100%)**	**51% (5%-100%)**	**79% (7%-100%)**
Median time to ≥90% chimerism	**Day +30**	**Day +75**	**Day +90**
Median time to ≥95% chimerism	**Day +60**	**Day +75**	**Day +105**

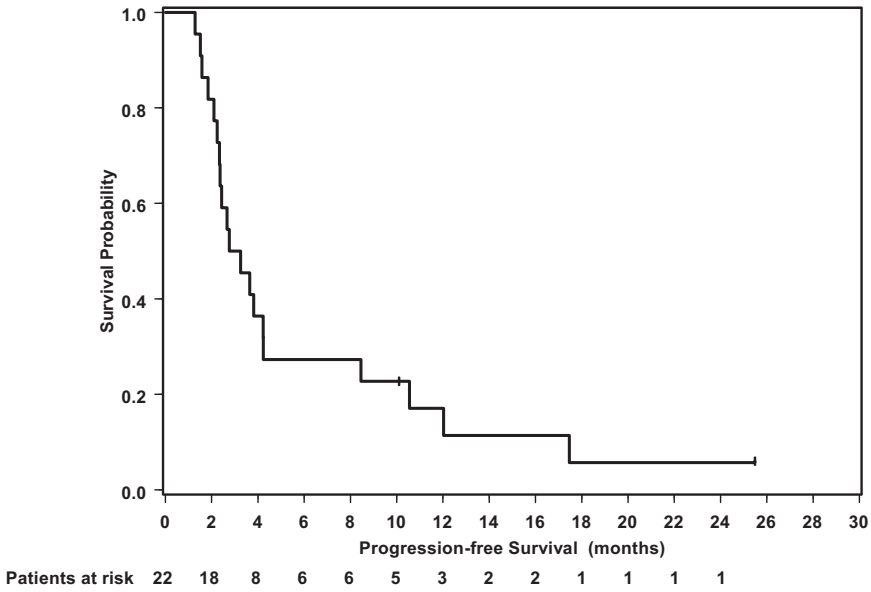

Figure 1. Kaplan-Meier progression-free survival for patients with metastatic RCC after N-SCT.

Clinical Outcomes

All 22 patients were evaluable for response, toxicity, and survival. No RECIST-defined objective responses were observed in 22 evaluable patients at any evaluation timepoints. Seventeen patients died, 15 patients died of disease progression, 1 of sepsis, and 1 of liver failure secondary to extensive GVHD. The remaining 5 patients are alive, 2 with stable disease and 3 with disease progression. Median progression-free survival was 3.0 months (95% CI, 2.3-4.2 months; Figure 1) and median overall survival was 5.5 months (95% CI, 3.9-12.0 months; Figure 2). DLI and subsequent interferon were administered to 2 patients; neither had an objective disease response or significant toxicity. The remaining patients were ineligible for DLI interferon because of rapid progression of disease or persistence of GVHD, which excluded patients from these maneuvers per protocol.

Toxicity

Acute toxicity was as expected from an N-SCT regimen, with typical myelosuppresion and grade 3 febrile neutropenia in 4 patients. Maximum grade ≥2 overall hematologic toxicity observed was grade 3 in 2 patients and grade 4 in 16 patients. Maximum nonhematologic toxicity observed was grade 3 in 8 patients, grade 4 in 8 patients, and grade 5 in 2 patients. Regimen-related mortality was reported in 2 of 22 patients (9%; 95%

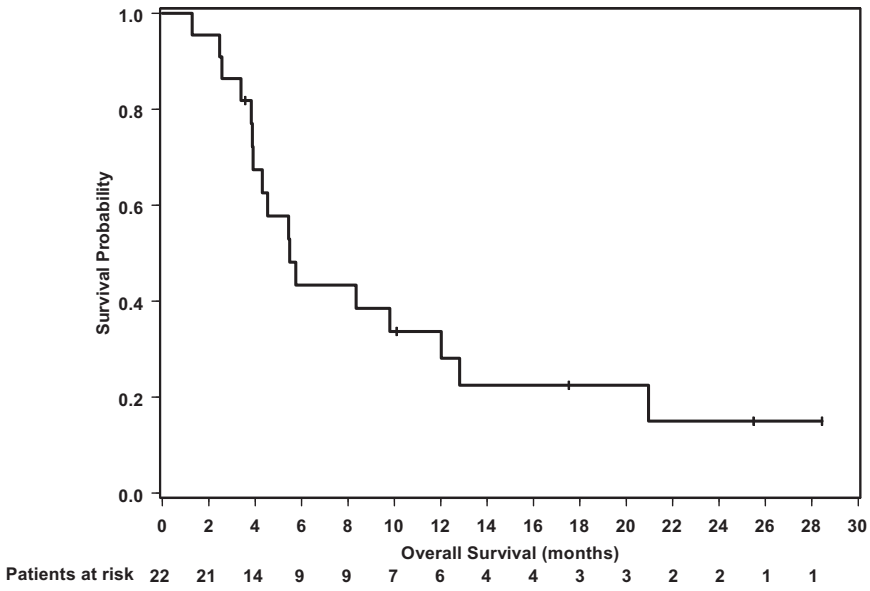

Figure 2. Kaplan-Meier overall survival for patients with metastatic RCC after N-SCT.

Table 4. *Graft-versus-Host Disease (n = 22)*

	Patients, n (%)
Acute GVHD	**11 (50%)**
Grade 1	**4 (18%)**
Grade 2	**4 (18%)**
Grade 3	**3 (14%)**
Grade 4	**0 (0%)**
Chronic GVHD	**5 (23%)**
Limited	**3 (14%)**
Extensive	**2 (9%)**

CI, 1%-29%), with 1 death from sepsis and 1 death from liver failure due to chronic GVHD.

Acute GVHD was observed in 11 patients (50%; 95% CI, 28%-72%) and was grade 2 in 4 patients (18%) and grade 3 in 3 patients (14%; Table 4). Acute GVH consisted of rash, diarrhea, and increased bilirubin. Chronic GVHD was observed in 5 patients. Chronic GVHD was limited in 3 patients and extensive in 2 patients. Of the 2 patients with extensive chronic GVHD, 1 died from liver failure and the other is alive with stable disease and ongoing chronic GVHD.

DISCUSSION

Based on previous studies of allogeneic SCT in metastatic RCCs demonstrating an antitumor effect, a multi-institutional study of this approach was undertaken to more accurately define the relative risks and benefits. No objective response was observed in this cohort. Toxicity included acute and chronic forms of GVHD with a 9% transplant-related mortality rate.

This study demonstrated that allogeneic SCT for metastatic RCC is feasible in a multi-institutional setting. Transplantation of solid tumors is unique from hematologic malignancies because it requires coordination between the solid tumor specialist, who may not otherwise have transplantation expertise, and the transplantation physician, who may not routinely care for patients with RCC. Thus, selection of patients with appropriate RCC disease features and timely delivery of N-SCT is paramount. Enrollment restriction to centers with expertise in RCC and transplantation allowed for successful evaluation of this approach in RCC. Nevertheless, inherent delays in the transplantation process including insurance approval and coordination of care may have resulted in worsening of disease before N-SCT and thus affected outcome. In addition, a substantial percentage of patients in this study had features of poor prognosis for RCC including previous radiotherapy, multiple sites of disease including hepatic metastases, multiple previous systemic treatment regimens, and a worse performance status compared with single-institution studies of N-SCT in RCC. Although complete data to characterize this cohort as reported for previously treated patients with metastatic RCC [17] was not available and direct comparison with other study cohorts is imprecise, the adverse features noted above may have decreased the ability to observe an antitumor effect from this therapy. The extremely short median progression-free and overall survivals observed for this cohort may reflect a patient group with a poor prognosis regardless of treatment. Lack of an observed antitumor effect thus highlights the appropriate but extreme selection of patients in previous single-institution studies and emphasizes the limited general applicability of this approach.

Because T cells are thought to mediate the graft-versus-renal cancer effect of N-SCT, establishment of a donor T-cell graft is required to allow for an antitumor effect before disease progression. Early and adequate donor T-cell engraftment was achieved in this study as manifest by chimerism assays and observation of GVHD. The GVHD prophylaxis regimen (tacrolimus and mini-methotrexate) is considered moderately immunosuppressive. Alternative, less immunosuppressive regimens could have resulted in more GVHD and possibly a greater GVT effect. However, most patients on this study developed acute and/or chronic GVHD without a significant GVT effect. Thus, the role of patient selection and a different therapeutic approach may be more important than degree of GVHD prophylactic immunosuppression. Previous series have noted acute and chronic GVHD in most, but not all, patients who develop tumor regression. Thus, separation of T cells directed against self versus tumor antigens would be a critical first step in favorably affecting the balance of risk and benefit of N-SCT in RCC. Further, recent in vitro data have suggested enhanced cytotoxicity against RCC cell lines using allogeneic killer immunoglobulin-like receptor–incompatible natural killer cells [18]. As further refinement of N-SCT for RCC is a reasonable investigative endeavor, a greater understanding of the specific cells mediating the GVT effect could allow for more efficient and safe application of this approach in RCC.

This study has several limitations. Patients were not as highly selected in terms of performance status, tumor burden, or pace of disease progression as in single-institution studies. Although this may have decreased the antitumor effect, such patients are more representative of the RCC population at large. Previous large studies of patients with metastatic RCC have identified several factors as prognostic of outcome [17,19-21]. It is clear that patient selection, especially in single-arm phase II trials, can heavily influence results. Patients selected for transplantation should be limited to those without adverse prognostic features. Such patient selection, which was not undertaken in this trial, will be paramount if this modality is to be

further investigated in RCC. Further, central histologic review was not undertaken to ensure clear cell histology; thus, inclusion of patients with non–clear cell histology could have diluted the antitumor effect. Data published subsequent to the design of this trial have indicated that the vast majority of responders to N-SCT in RCC have clear cell histology. Moreover, management of a GVH response was left to the discretion of the treating physician. Currently, a balance between GVH and GVT effects may be delicate, and variable handling of immunosuppressive regimens could have affected outcome.

The clinical necessity of this high-risk approach has also lessened recently. Approaches targeting vascular endothelial growth factor in metastatic RCC have demonstrated substantial clinical activity with acceptable safety profiles [22-24]. These approaches are likely to assume a significant role in the therapy of advanced RCC. In addition, the modest activity of cytokines will continue their use in advanced RCC. Thus, the risk-benefit profile of N-SCT in RCC would relegate this approach to patients refractory to these treatments, potentially diminishing the suitability of such patients for transplantation and lessening the chance of observing an antitumor effect. In summary, a GVT effect was not observed in this study despite acute and chronic GVHDs, thus highlighting the need for further understanding of this approach. Allogeneic SCT remains investigational in RCC.

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